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TITLE OF THE INVENTION (280 characters max)

M3 MUSCARINIC ACETYLCHOLINE RECEPTOR ANTAGONISTS

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Date: 3/11/04
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Novel M_3 Muscarinic Acetylcholine Receptor Antagonists

FIELD OF THE INVENTION

This invention relates to novel derivatives of biaryl quaternary ammonium salts, pharmaceutical compositions, processes for their preparation, and use thereof in treating M_3 muscarinic acetylcholine receptor mediated diseases.

BACKGROUND OF THE INVENTION

Acetylcholine released from cholinergic neurons in the peripheral and central nervous systems affects many different biological processes through interaction with two major classes of acetylcholine receptors – the nicotinic and the muscarinic acetylcholine receptors. Muscarinic acetylcholine receptors (mAChRs) belong to the superfamily of G-protein coupled receptors that have seven transmembrane domains. There are five subtypes of mAChRs, termed M_1-M_5, and each is the product of a distinct gene. Each of these five subtypes displays unique pharmacological properties. Muscarinic acetylcholine receptors are widely distributed in vertebrate organs, and these receptors can mediate both inhibitory and excitatory actions. For example, in smooth muscle found in the airways, bladder and gastrointestinal tract, M_3 mAChRs mediate contractile responses. For review, please see {Brown 1989 247 /id}.

Muscarinic acetylcholine receptor dysfunction has been noted in a variety of different pathophysiological states. For instance, in asthma and chronic obstructive pulmonary disease (COPD), inflammatory conditions lead to loss of inhibitory M_2 muscarinic acetylcholine autoreceptor function on parasympathetic nerves supplying the pulmonary smooth muscle, causing increased acetylcholine release following vagal nerve stimulation. This mAChR dysfunction results in airway hyperreactivity mediated by increased stimulation of M_3 mAChRs{Costello, Evans, et al. 1999 72 /id}{Minette, Lammers, et al. 1989 248 /id}. Similarly, inflammation of the gastrointestinal tract in

inflammatory bowel disease (IBD) results in M_3 mAChR-mediated hypermotility {Oprins, Meijer, et al. 2000 245 /id}. Incontinence due to bladder hypercontractility has also been demonstrated to be mediated through increased stimulation of M_3 mAChRs {Hegde & Eglen 1999 251 /id}. Thus the identification of subtytpe-selective mAChR antagonists may be useful as therapeutics in these mAChR-mediated diseases.

Despite the large body of evidence supporting the use of anti-muscarinic receptor therapy for treatment of a variety of disease states, relatively few anti-muscarinic compounds are in use in the clinic. Thus, there remains a need for novel compounds that are capable of causing blockade at M_3 mAChRs. Conditions associated with an increase in stimulation of M_3 mAChRs, such as asthma, COPD, IBD and urinary incontinence would benefit by compounds that are inhibitors of mAChR binding.

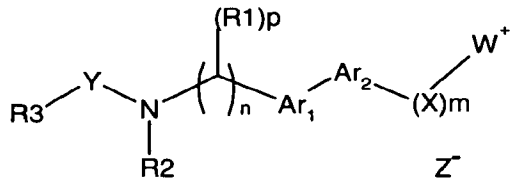
SUMMARY OF THE INVENTION

This invention provides for a method of treating a muscarinic acetylcholine receptor (mAChR) mediated disease, wherein acetylcholine binds to an M_3 mAChR and which method comprises administering an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

This invention also relates to a method of inhibiting the binding of acetylcholine to its receptors in a mammal in need thereof which comprises administering to aforementioned mammal an effective amount of a compound of Formula (I).

The present invention also provides for the novel compounds of Formula (I), and pharmaceutical compositions comprising a compound of Formula (I), and a pharmaceutical carrier or diluent.

Compounds of Formula (I) useful in the present invention are represented by the structure:



(I)

wherein

Ar1 and Ar2, are independently, selected from the group consisting of optionally substituted phenyl and optionally substituted monocyclic heteroaryl;

W^+ is $N^+R_6R_7R_8$, or an optionally substituted saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more quaternary ammonium nitrogens, and optionally contain one or more O, or S;

Z^- is a pharmaceutically acceptable counter ion, selected from the group consisting of I^-, Br^-, Cl^-, F^-, $CF3COO^-$, mesylate, and tosylate;

X is C(R1)p, or C(O); wherein, when X is C(R1)p, m is an interger from 0 to 3; when X is C(O), m is 1;

p is an interger from 0 to 2;

n is an interger from 0 to 3;

Y is C(O), S(O)q, HNC(O), or OC(O); wherein, q is 1 or 2;

R1 and R2, are independently, selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted heterocylic, optionally substituted heterocyclicalkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aryl alkyl, optionally substituted heteroaryl, and optionally substituted heteroaryl alkyl;

R3 is selected from the group consisting of optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkenyl, optionally substituted C_1-C_{10} alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted aryl alkyl, and

optionally substituted heteroaryl alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of halogen, cyano, hydroxy, hydroxy substituted C_{1-10}alkyl, C_{1-10} alkoxy, $S(O)_{m'}$ C_{1-10} alkyl, C(O)R4, $C(O)NR_4R_5$; C(O)OH; $S(O)_2NR_4R_5$, $NHC(O)R_4$, $NHS(O)_2R_4$, C_{1-10} alkyl, alkenyl, halosubstituted C_{1-10} alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroaryl alkyl, wherein these aryl or heteroaryl moieties may be substituted one to two times by halogen, hydroxy, hydroxy substituted alkyl, C_{1-10} alkoxy, $S(O)_{m'}C_{1-10}$ alkyl, C_{1-10} alkyl, or halosubstituted C_{1-10} alkyl;

m' is 0, 1, or 2;

R_4 and R_5, are independently, selected from the group consisting of hydrogen, optionally substituted C_{1-10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted aryl, optionally substituted aryl alkyl, optionally substituted heteroaryl, and optionally substituted heteroaryl alkyl; or R_4 and R_5 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O, and S; and

R_6, R_7, and R_8, are independently, selected from the group consisting of hydrogen, optionally substituted C_{1-10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, and optionally substituted heterocyclicalkyl; or R_7 and R_8 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O, N and S;

or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION

The present invention includes all hydrates, solvates, complexes and prodrugs of the compounds of this invention. Prodrugs are any covalently bonded compounds that release the active parent drug according to Formula I - **in vivo**. If a chiral center or another form of an isomeric center is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and diastereomers, are intended to be covered herein. Inventive compounds containing a chiral center may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone. In cases in which compounds have unsaturated carbon-carbon double bonds, both the cis (Z) and trans (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

The meaning of any substituent at any one occurrence in Formula I or any subformula thereof is independent of its meaning, or any other substituent's meaning, at any other occurrence, unless specified otherwise.

Abbreviations and symbols commonly used in the peptide and chemical arts are used herein to describe the compounds of the present invention. In general, the amino acid abbreviations follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature as described in **Eur. J. Biochem.**, 158, 9 (1984).

For use herein the term "the aryl, heteroaryl, and heterocyclic containing moieties" refers to both the ring and the alkyl, or if included, the alkenyl rings,

such as aryl, arylalkyl, and aryl alkenyl rings. The term "moieties" and "rings" may be interchangeably used throughout.

As used herein, "optionally substituted" unless specifically defined shall mean such groups as hydrogen; halogen, such as fluorine, chlorine, bromine or iodine; cyano; hydroxy; hydroxy substituted C_{1-10}alkyl; C_{1-10} alkoxy, such as methoxy or ethoxy; $S(O)_{m'}$ C_{1-10} alkyl, wherein m' is 0, 1 or 2, such as methyl thio, methyl sulfinyl or methyl sulfonyl; amino, mono & di-substituted amino, such as in the NR_7R_8 group; $NHC(O)R_7$; $C(O)NR_7R_8$; C(O)R7; C(O)OH; $S(O)_2NR_7R_8$; $NHS(O)_2R_7$; C_{1-10} alkyl, such as methyl, ethyl, propyl, isopropyl, or t-butyl; alkenyl, such as ethenyl, 1-propenyl, 2-propenyl, or 2-methyl-1-propenyl; halosubstituted C_{1-10} alkyl, such CF_3; an optionally substituted aryl, such as phenyl, or an optionally substituted arylalkyl, such as benzyl or phenethyl, optionally substituted heterocylic, optionally substituted heterocyclic alkyl, optionally substituted heteroaryl, optionally substituted heteroaryl alkyl, wherein these aryl , heteroaryl, or heterocyclic moieties may be substituted one to two times by halogen; hydroxy; hydroxy substituted alkyl; C_{1-10} alkoxy; $S(O)_{m'}C_{1-10}$ alkyl; amino, mono & di-substituted alkyl amino, such as in the NR_7R_8 group; C_{1-10} alkyl, or halosubstituted C_{1-10} alkyl, such as CF_3.

Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane sulphonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid and mandelic acid.

The following terms, as used herein, refer to:

- "halo" or "halogen" - chloro, fluoro, bromo and iodo.
- "C_{1-10}alkyl" or "alkyl" - both straight and branched chain moieties of 1 to 10 carbon atoms, unless the chain length is otherwise limited, including, but

not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl and the like.

- "C_1-C_{10} alkoxy" includes straight and branched chain radicals of the likes of -O-CH_3, -O-CH_2CH_3, and the n-propoxy, isopropoxy, n-butoxy, sec-butoxy, isobutoxy, *tert*-butoxy, pentoxy, and hexoxy, and the like.
- " C_3-C_{10} cycloalkyl" is used herein to mean cyclic moiety, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, and the like.
- "alkenyl" is used herein at all occurrences to mean straight or branched chain moiety of 2-10 carbon atoms, unless the chain length is limited thereto, including, but not limited to ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.
- "aryl" - phenyl and naphthyl;
- "heteroaryl" (on its own or in any combination, such as "heteroaryloxy", or "heteroaryl alkyl") - a 5-10 membered aromatic ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O or S, such as, but not limited, to pyrrole, pyrazole, furan, thiophene, quinoline, isoquinoline, quinazolinyl, pyridine, pyrimidine, oxazole, tetrazole, thiazole, thiadiazole, triazole, imidazole, or benzimidazole.
- "heterocyclic" (on its own or in any combination, such as "heterocyclicalkyl") - a saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O, or S; such as, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, tetrahydropyran, thiomorpholine, or imidazolidine. Furthermore, sulfur may be optionally oxidized to the sulfone or the sulfoxide.
- "secondary nitrogen" is used herein to mean a nitrogen directly connected to one hydrogen, one optionally substituted carbon, and one optionally substituted carbon, C(O), or S(O)m'; where in m' is 1 or 2.

• "tertiary nitrogen" is used herein to mean a nitrogen directly connected to two independent optionally substituted carbons, and one optionally substituted carbon, C(O), or S(O)m'; where in m' is 1 or 2.

• "arylalkyl" or "heteroarylalkyl" or "heterocyclicalkyl" is used herein to mean C_{1-10} alkyl, as defined above, attached to an aryl, heteroaryl or heterocyclic moiety, as also defined herein, unless otherwise indicated.

• "sulfinyl" - the oxide S (O) of the corresponding sulfide, the term "thio" refers to the sulfide, and the term "sulfonyl" refers to the fully oxidized $S(O)_2$ moiety.

The preferred compounds of Formula I include those compounds wherein:

Ar1 and Ar2, are independently, selected from the group consisting of optionally substituted phenyl and optionally substituted monocyclic heteroaryl;

W^+ is an optionally substituted saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more quaternary ammonium nitrogens;

Z^- is a pharmaceutically acceptable counter ion, selected from the group consisting of I^-, Br^-, Cl^-, F^-, $CF3COO^-$, mesylate, and tosylate;

X is C(R1)p, m is 1;

p is 2;

n is an interger from 1 to 3;

Y is C(O), or S(O)q;wherein, q is 1 or 2;

R1 is hydrogen;

R2 is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted heterocylic, optionally substituted heterocyclicalkyl, optionally

substituted aryl, optionally substituted aryl alkyl, optionally substituted heteroaryl, and optionally substituted heteroaryl alkyl;

R3 is selected from the group consisting of optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkenyl, optionally substituted C_1-C_{10} alkyl, optionally substituted C_3-C_{10} cycloalkyl, and optionally substituted C_3-C_{10} cycloalkyl alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of halogen, cyano, hydroxy, hydroxy substituted C_{1-10}alkyl, C_{1-10} alkoxy, $S(O)_{m'}$ C_{1-10} alkyl, C(O)R4, $C(O)NR_4R_5$; C(O)OH; $S(O)_2NR_4R_5$, $NHC(O)R_4$, $NHS(O)_2R_4$, C_{1-10} alkyl, alkenyl, halosubstituted C_{1-10} alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroaryl alkyl, wherein these aryl or heteroaryl moieties may be substituted one to two times by halogen, hydroxy, hydroxy substituted alkyl, C_{1-10} alkoxy, $S(O)_{m'}C_{1-10}$ alkyl, C_{1-10} alkyl, or halosubstituted C_{1-10} alkyl; and m' is 0, 1, or 2;

R_4 and R_5, are independently, selected from the group consisting of hydrogen, optionally substituted C_{1-10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted aryl, optionally substituted aryl alkyl, optionally substituted heteroaryl, and optionally substituted heteroaryl alkyl; or R_4 and R_5 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O, and S; and

R_7 and R_8, are independently, selected from the group consisting of hydrogen, optionally substituted C_{1-10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl,

optionally substituted heterocyclic, and optionally substituted heterocyclicalkyl; or R_7 and R_8 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O, N and S;

or a pharmaceutically acceptable salt thereof.

Even more preferred are those compounds where:

Ar1 and Ar2, are independently, optionally substituted phenyl;

W^+ is an optionally substituted saturated or partially unsaturated 5-8 membered ring system in which one or more rings contain one or more quaternary ammonium nitrogens;

Z^- is a pharmaceutically acceptable counter ion, selected from the group consisting of I^-, Br^-, Cl^-, F^-, $CF3COO^-$, mesylate, and tosylate;

X is C(R1)p;

R1 is hydrogen

p is 2;

m is 1;

n is 1;

Y is C(O), or S(O)q; wherein, q is 1 or 2;

R2 is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted heterocylic, optionally substituted heterocyclicalkyl, optionally substituted aryl alkyl, and optionally substituted heteroaryl alkyl;

R3 is selected from the group consisting of optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkenyl, optionally substituted C_1-C_{10} alkyl, optionally substituted C_3-C_{10} cycloalkyl, and optionally substituted C_3-C_{10} cycloalkyl alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting

of halogen, cyano, hydroxy, hydroxy substituted C_{1-10}alkyl, C_{1-10} alkoxy, $S(O)_{m'}$ C_{1-10} alkyl, C(O)R4, $C(O)NR_4R_5$; C(O)OH; $S(O)_2NR_4R_5$, $NHC(O)R_4$, $NHS(O)_2R_4$, C_{1-10} alkyl, alkenyl, and halosubstituted C_{1-10} alkyl; wherein m' is 0, 1, or 2;

R_4 and R_5, are independently, selected from the group consisting of hydrogen, optionally substituted C_{1-10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted aryl, optionally substituted aryl alkyl, optionally substituted heteroaryl, and optionally substituted heteroaryl alkyl; or R_4 and R_5 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O, and S; and

R_7 and R_8, are independently, selected from the group consisting of hydrogen, optionally substituted C_{1-10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, and optionally substituted heterocyclicalkyl; or R_7 and R_8 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O, N and S;

or a pharmaceutically acceptable salt thereof.

Illustrative compounds of Formula (I) include:

1-methyl-1-({3'-[({[4-(methyloxy)phenyl]sulfonyl}amino)methyl]-3-biphenylyl}methyl)piperidinium trifluoroacetate;

1-[(3'-{[(1,3-benzodioxol-5-ylcarbonyl)amino]methyl}-3-biphenylyl)methyl]-1-methylpiperidinium trifluoroacetate;

1-[(3'-{[(1,3-benzodioxol-5-ylcarbonyl)amino]methyl}-3-biphenylyl)methyl]-1-methylpiperazin-1-ium trifluoroacetate - trifluoroacetic acid (1:1);

1,1-dimethyl-4-({3'-[({[4-(methyloxy)phenyl]sulfonyl}amino)methyl]-3-biphenylyl}methyl)piperazin-1-ium trifluoroacetate - trifluoroacetic acid (1:1);

4-[(3'-{[(1,3-benzodioxol-5-ylcarbonyl)amino]methyl}-3-biphenylyl)methyl]-1,1-dimethylpiperazin-1-ium trifluoroacetate - trifluoroacetic acid (1:1);

1-[(3'-{[(1,3-benzodioxol-5-ylcarbonyl)amino]methyl}-3-biphenylyl)methyl]-1-methyl-3-oxopiperazin-1-ium trifluoroacetate;

4-[(3'-{[(1,3-benzodioxol-5-ylcarbonyl)amino]methyl}-3-biphenylyl)carbonyl]-1,1-dimethylhexahydro-1*H*-1,4-diazepin-1-ium trifluoroacetate - trifluoroacetic acid (1:1); and

4-{[3'-({[(3-cyanophenyl)carbonyl]amino}methyl)-3-biphenylyl]methyl}-1,1-dimethylpiperazin-1-ium trifluoroacetate - trifluoroacetic acid (1:1);

or any other pharmaceutically acceptable counter ion and/or salt.

Methods of Preparation

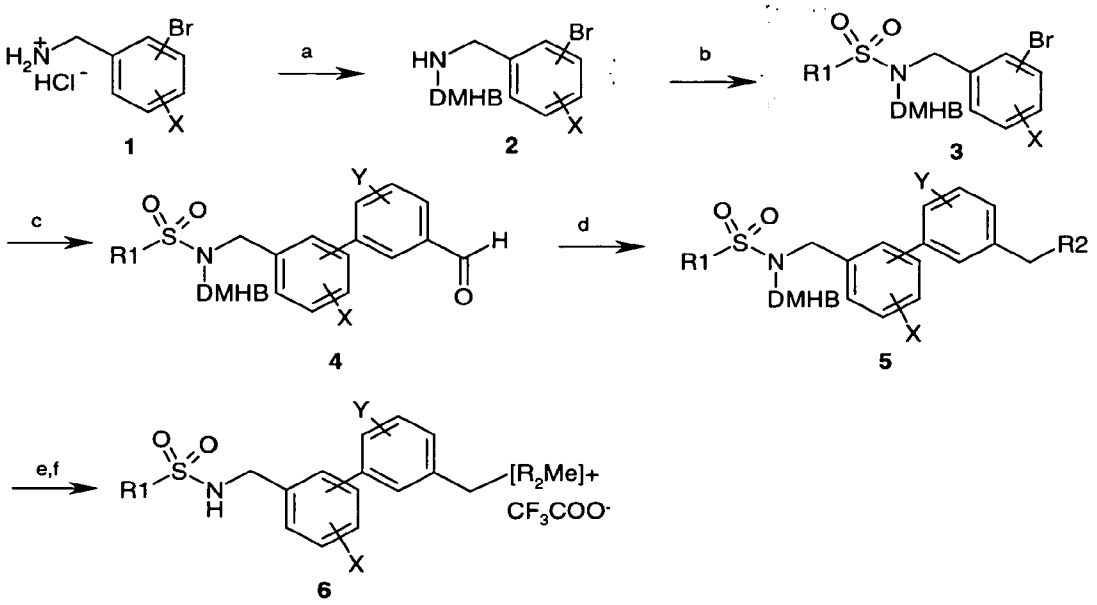
Preparation

The compounds of Formula (I) may be obtained by applying synthetic procedures, some of which are illustrated in the Schemes below. The synthesis provided for these Schemes is applicable for producing compounds of Formula (I) having a variety of different R1 and R2, which are reacted, employing substituents which are suitable protected, to achieve compatibility with the reactions outlined herein. Subsequent deprotection, in those cases, then affords compounds of the nature generally disclosed. While some Schemes are shown with specific compounds, this is merely for illustration purpose only.

Preparation 1

As shown in Scheme 1, bromo benzylamines **1** were loaded onto 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde (DMHB resin) via reductive alkylation. The resin-bound amines **2** were reacted with various sulfonyl chlorides to yield sulfonamides **3**, which underwent Suzuki coupling with substituted formyl phenyl boronic acids to give biphenylaldehydes **4**. Reductive alkylation of **4** with amines afforded biphenyl amines **5**, which were reacted with methyl iodide, followed by cleavage with 20% of trifluoroacetic acid in dichoroethane, afforded desired quaternary ammonium salts **6**.

Scheme 1



Conditions: a) DMHB resin, $Na(OAc)_3BH$, diisopropylethylamine, acetic acid, 1-methyl-2-pyrrolidinone, rt; b) $R1SO_2Cl$, pyridine, dichloroethane, rt; c) substituted formyl phenyl-boronic acids, $Pd(PPh_3)_4$, K_2CO_3, dimethoxyethane, 80°C; d) R2 amine, $Na(OAc)_3BH$, Na_2SO_4, dichloroethane, rt; e) methyl iodide (MeI), MeCN, rt; f) 20% of trifluoroacetic acid in dichoroethane, rt.

SYNTHETIC EXAMPLES

The following examples are provided as illustrative of the present invention but not limiting in any way:

Example 1

Preparation of 1-methyl-1-({3'-[({[4-(methyloxy)phenyl]sulfonyl}amino)methyl]-3-biphenylyl}methyl)piperidinium trifluoroacetate

a) DMHB resin-bound 3-bromo-benzylamine

To a 250 mL shaker vessel was added 2,6-dimethoxy-4-polystyrenebenzyloxy-benzaldehyde (DMHB resin) (10 g, 1.5 mmol/g, 15 mmol) and 150 mL of 1-methyl-2-pyrrolidinone (NMP). 3-Bromo-benzylamine HCl salt (17 g, 75 mmol), diisopropylethylamine (DIEA) (13 mL, 75 mmol), acetic acid (HOAc) (15 mL), and $Na(OAc)_3BH$ (19.1 g, 90 mmol) were then added. The resulting mixture was shaken at rt for overnight, and was then washed with NMP (150 mL x 2), dichloromethane (DCM) (150 mL x 2), MeOH (150 mL x 2) and DCM (150 mL x 2). The resulting resin was dried in vacuum oven at 35 °C for overnight to yield DMHB resin-bound 3-bromo-benzylamine (15 mmol).

b) 1-Methyl-1-({3'-[({[4-(methyloxy)phenyl]sulfonyl}amino)methyl]-3-biphenylyl}methyl)piperidinium trifluoroacetate

To a mixture of the above resin-bound 3-bromo-benzylamine (**1a**, 2 g, 1.2 mmol/g (theoretical loading), 2.4 mmol) in 80 mL of dichloroethane (DCE) was added 4-methoxybenzenesulfonyl chloride (5.0 g, 24 mmol) and pyridine (13 mL, 160 mmol). The mixture was shaken at rt for overnight, and was then washed with DCM (100 mL x 2), MeOH (100 mL x 2) and DCM (100 mL x 2). The resulting resin was dried in vacuum oven at 35 °C for overnight. An analytical amount of the resin was cleaved with 20% of trifluoroacetic acid in

DCE for 10 min. The resulting solution was concentrated *in vacuo* and dissolved in 0.5 mL of MeOH. MS (ESI): 356 $[M+H]^+$.

To a mixture of the above resin-bound *N*-[(3-bromophenyl)methyl]-4-(methyloxy)benzenesulfonamide (3.38 g, 0.99 mmol/g (theoretical loading), 3.35 mmol) in 83 mL of dimethoxyethane (DME) was added 3-formylphenyl boronic acid (1.49 g, 9.93 mmol), 2 M K_2CO_3 aqueous solution (5 mL, 9.93 mmol) and $Pd(PPh_3)_4$ (0.19 g, 0.17 mmol). After purged with argon for 5-10 min, the mixture was heated at 80 °C for 10 h under argon. The resin was then washed with tetrahydrofuran (THF) (100 mL x 2), THF:H_2O (1:1, 100 mL x 2), H_2O (100 mL x 2), THF:H_2O (1:1, 100 mL x 2), THF (100 mL x 2), DCM (100 mL x 2), and dried in vacuum oven at 35 °C for overnight. An analytical amount of the resin was cleaved with 20% of TFA in DCE for 10 min. The resulting solution was concentrated *in vacuo* and dissolved in 0.5 mL of CH_3CN. MS (ESI): 382 $[M+H]^+$.

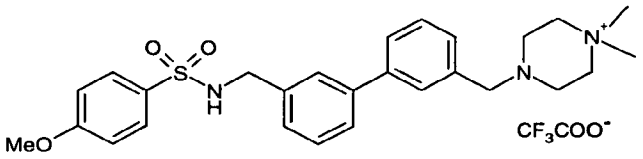
To a mixture of the above resin-bound *N*-[(3'-formyl-3-biphenylyl)methyl]-4-(methyloxy)benzenesulfonamide (50 mg, 0.97 mmol/g (theoretical loading), 0.0485 mmol) in 2mL mL of DCE was added Na_2SO_4 (60 mg, 0.42 mmol) and piperidine (41 uL, 0.42 mmol). After shaking at rt for 10 min, $Na(OAc)_3BH$ (98 mg, 0.46 mmol) was added. The mixture was shaken at rt for overnight. The resulting resin was washed with THF (10 mL x 2), THF:H_2O (1:1, 10 mL x 2), H_2O (10 mL x 2), THF:H_2O (1:1, 10 mL x 2), THF (10 mL x 2), DCM (10 mL x 2), and dried in vacuum oven at 35 °C for overnight. An analytical amount of the resin was cleaved with 20% of TFA in DCE for 10 min. The resulting solution was concentrated *in vacuo* and dissolved in 0.5 mL of MeOH. MS (ESI): 451$[M+H]^+$.

To a mixture of the above resin-bound 4-(methyloxy)-*N*-{[3'-(1-piperidinylmethyl)-3-biphenylyl]methyl}benzenesulfonamide (50 mg, 0.91 mmol/g (theoretical loading), 0.0455 mmol) in 6 mL of CH_3CN was added methyl iodide (MeI) (0.05 mL). The mixture was shaken at rt for overnight. The

resin was washed with CH_3CN (10 mL x 2), DCM (10 mL x 2), MeOH (10 mL x 2), DCM (10 mL x 2), and dried in vacuum oven at 35°C for overnight. The resulting resin was cleaved with 2 mL of 20% of TFA in DCE for 30 min and treated again with 2 mL of 20% of TFA in DCE for 30 min. The combined cleavage solution was concentrated *in vacuo*. The residue was dissolved in DMSO and purified using a Gilson semi-preparative HPLC system with a YMC ODS-A (C-18) column 50 mm by 20 mm ID, eluting with 10% B to 90% B in 3.2 min, hold for 1 min where A = H_2O (0.1% trifluoroacetic acid) and B = CH_3CN (0.1% trifluoroacetic acid) pumped at 25 mL/min, to produce 1-methyl-1-({3'-[({[4-(methyloxy)phenyl]sulfonyl}amino)methyl]-3-biphenylyl}methyl)piperidinium trifluoroacetate (white powder, 8 mg, 38% over 6 steps). MS (ESI): 465 $[M]^+$.

Proceeding in a similar manner, but replacing piperidine with 1-methylpiperazine, the following compound in Table 1 was prepared.

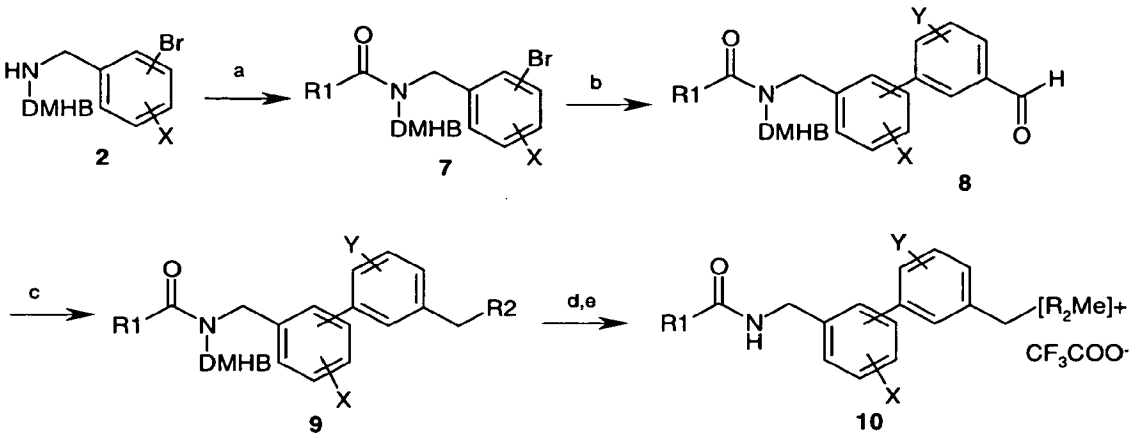
Table 1

Example	Compound	MS $[M]^+$
2		480

Preparation 2

The resin-bound bromobenzylamines **2** were reacted with acids to yield amides **7**, which underwent Suzuki coupling with substituted formyl phenyl boronic acids to give biphenylaldehydes **8** (Scheme 2). Reductive alkylation of **8** with amines afforded biphenyl amines **9**, which were treated with MeI, followed by cleavage, produced the desired quaternary ammonium salts **10**.

Scheme 2



Conditions: a) $R1CO_2H$, 1,3-diisopropylcarbodiimide (DIC), DCM:dimethylforamide (DMF) = 1:1, rt; b) various formyl phenyl-boronic acids, $Pd(PPh_3)_4$, K_2CO_3, DME, 80°C; c) R2 amine, $Na(OAc)_3BH$, Na_2SO_4, DCM, rt; d) MeI, MeCN, rt; e) 20% of TFA in DCE, rt.

Example 3

Preparation of 1-[(3'-{[(1,3-benzodioxol-5-ylcarbonyl)amino]methyl}-3-biphenylyl)methyl]-1-methylpiperidinium trifluoroacetate

a) DMHB resin-bound *N*-[(3-bromophenyl)methyl]-1,3-benzodioxole-5-carboxamide

To a mixture of DMHB resin-bound 3-bromo-benzylamine (**1a**, 2 g, 1.2 mmol/g (theoretical loading), 2.4 mmol) in DCE/DMF (1:1, 80 mL) was added piperonylic acid (4.0 g, 24 mmol) and DIC (3.7 mL, 24 mmol). The mixture was shaken at rt for overnight and was then washed with DMF (100 mL x 2), DCM (100 mL x 2), MeOH (100 mL x 2) and DCM (100 mL x 2). The resulting resin was dried in vacuum oven at 35 °C for overnight to yield DMHB resin-bound *N*-[(3-bromophenyl)methyl]-1,3-benzodioxole-5-carboxamide (2.4 mmol). An analytical amount of the resin was cleaved with 20% of TFA in DCE for 10 min. The resulting solution was concentrated *in vacuo* and dissolved in 0.5 mL of MeOH. MS (ESI): 334 $[M+H]^+$.

b) 1-[(3'-{[(1,3-Benzodioxol-5-ylcarbonyl)amino]methyl}-3-biphenylyl)methyl]-1-methylpiperidinium trifluoroacetate

To a mixture of DMHB resin-bound *N*-[(3-bromophenyl)methyl]-1,3-benzodioxole-5-carboxamide (**3a**, 3.03 g, 1.0 mmol/g (theoretical loading), 3.03 mmol) in 76 mL of DME was added 3-formylphenyl boronic acid (1.36 g, 9.09 mmol), 2 M K_2CO_3 aqeous solution (4.5 mL, 9.09 mmol), and $Pd(PPh_3)_4$ (0.18 g, 0.15 mmol). After purged with argon for 5-10 min, the mixture was heated at 80 °C under argon for 10 h. The resulting resin was washed with THF (100 mL x 2), THF:H_2O (1:1, 100 mL x 2), H_2O (100 mL x 2), THF:H_2O (1:1, 100 mL x 2), THF (100 mL x 2), DCM (100 mL x 2), and dried in vacuum oven at 35 °C for overnight. An analytical amount of the resin was cleaved with 20% of TFA in DCM for 10 min. The resulting solution was concentrated *in vacuo* and dissolved in 0.5 mL of CH_3CN. MS (ESI): 360 $[M+H]^+$.

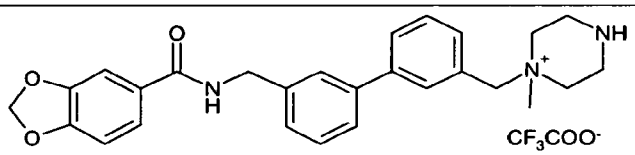
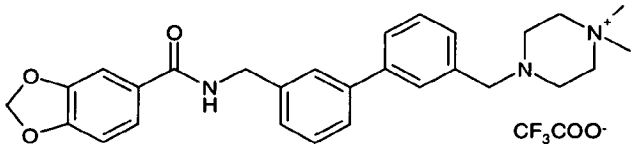
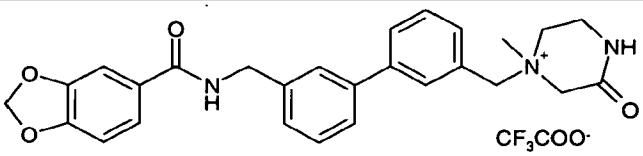
To a mixture of the above resin (50 mg, 0.99 mmol/g (theoretical loading), , 0.0495 mmol) in 2 mL of DCE was added Na_2SO_4 (60 mg, 0.42 mmol) and piperidine (41 uL, 0.42 mmol). After shaking for 10min, $Na(OAc)_3BH$ (98 mg, 0.46 mmol) was added. After shaken at rt for overnight, the resin was washed with THF (10 mL x 2), THF:H_2O (1:1, 10 mL x 2), H_2O (10 mL x 2), THF:H_2O (1:1, 10 mL x 2), THF (10 mL x 2), DCM (10 mL x 2) and dried in vacuum oven at 35 °C for overnight. An analytical amount of the resin was cleaved with 20% of TFA in DCM for 10 min. The resulting solution was concentrated *in vacuo* and dissolved in 0.5 mL of MeOH. MS (ESI): 429 $[M+H]^+$.

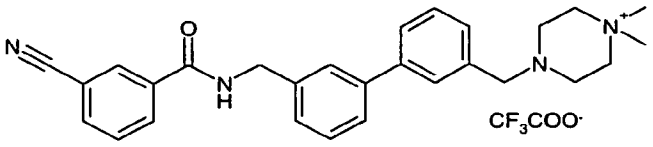
To a mixture of the above resin-bound *N*-{[3'-(1-piperidinylmethyl)-3-biphenylyl]methyl}-1,3-benzodioxole-5-carboxamide (50 mg, 0.93 mmol/g (theoretical loading), 0.0465 mmol) in 6 mL of CH_3CN was added MeI (0.05 mL). The mixture was shaken at rt for overnight. The resin was washed with CH_3CN (10 mL x 2), DCM (10 mL x 2), MeOH (10 mL x 2), DCM (10 mL x 2), and dried in vacuum oven at 35 °C for overnight. The resulting resin was

cleaved with 2 mL of 20% of TFA in DCE for 30 min and treated again with 2 mL of 20% of TFA in DCE for 30 min. The combined cleavage solution was concentrated *in vacuo*. The residue was dissolved in DMSO and purified using a Gilson semi-preparative HPLC system with a YMC ODS-A (C-18) column 50 mm by 20 mm ID, eluting with 10% B to 90% B in 3.2 min, hold for 1 min where A = H_2O (0.1% trifluoroacetic acid) and B = CH_3CN (0.1% trifluoroacetic acid) pumped at 25 mL/min, to produce 1-[(3'-{[(1,3-benzodioxol-5-ylcarbonyl)amino]methyl}-3-biphenylyl)methyl]-1-methylpiperidinium trifluoroacetate (white powder, 7 mg, 34% over 6 steps). MS (ESI): 443 $[M]^+$.

Proceeding in a similar manner, but replacing piperidine with the appropriate amines (e.g. 1,1-dimethylethyl 1-piperazinecarboxylate in example **4**, 1-methylpiperazine in example **5** and **7**, 2-piperazinone in example **6**), and/or replacing piperonylic acid with the appropriate acid, the compounds listed in Tables 2 were prepared.

Table 2

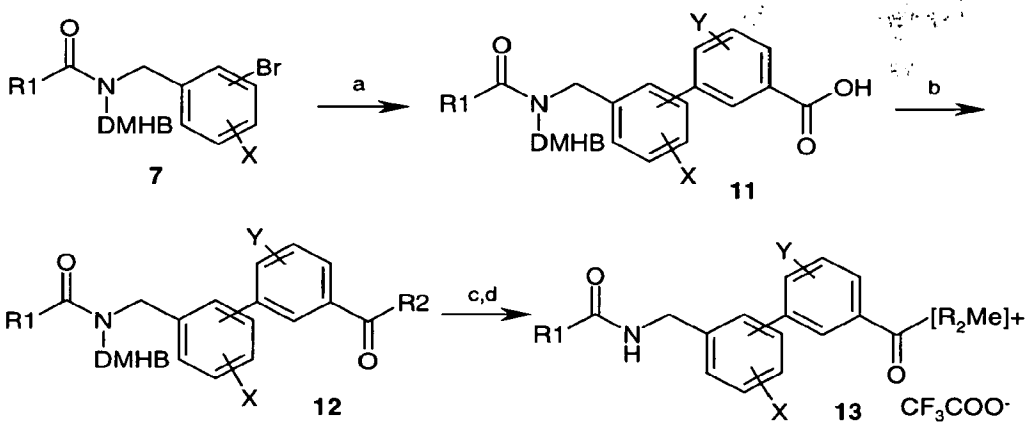
Example	Compound	MS $[M]^+$
4		444
5		458
6		458

7		439

Preparation 3

Resin-bound bromo benzylamides **7** underwent Suzuki coupling with dihydroxyboranyl benzoic acids to give biaryl acides **11** (Scheme 3). Amide formation of **11** with diamines yielded amides **12**, which were treated with MeI, followed by resin cleavage, afforded the desired quaternary ammonium salts **13**.

Scheme 3



Conditions: a) dihydroxyboranyl benzoic acids, 10% $Pd(PPh_3)_4$, Cs_2CO_3, DMF, 80 °C; b) R2 amine, PyBOP, DIEA, NMP, rt; c) MeI, MeCN, rt; d) 20% of TFA in DCE, rt.

Example 8

Preparation of 4-[(3'-{[(1,3-benzodioxol-5-ylcarbonyl)amino]methyl}-3-biphenylyl)carbonyl]-1,1-dimethylhexahydro-1*H*-1,4-diazepin-1-ium trifluoroacetate - trifluoroacetic acid (1:1)

To a mixture of DMHB resin-bound *N*-[(3-bromophenyl)methyl]-1,3-benzodioxole-5-carboxamide (**3a**, 1.3 g, 1.0 mmol/g (theoretical loading), 1.3 mmol) in 30 mL of DMF was added 3-(dihydroxyboranyl) benzoic acid (1.3 g, 7.8 mmol), 2 M $CsCO_3$ aqeous solution (1.95 mL, 3.9 mmol), and $Pd(PPh_3)_4$ (0.15 g, 0.13 mmol). The mixture was purged with argon for 5 min and was then heated at 80 °C for overnight. The resin was washed with DMF (50 mL), THF (50 mL x 2), THF:H_2O (1:1, 50 mL x 2), H_2O (50 mL x 2), THF:H_2O (1:1, 50 mL x 2), THF (50 mL x 2), DCM (50 mL x 2), and dried in vacuum oven at 35 °C for overnight. An analytical amount of the resin was cleaved with 20% of TFA in DCM for 10 min. The resulting solution was concentrated *in vacuo* and dissolved in 0.5 mL of MeOH. MS (ESI): 376 $[M+H]^+$.

To a mixture of the above resin bound 3'-{[(1,3-benzodioxol-5-ylcarbonyl)amino]methyl}-3-biphenylcarboxylic acid (100 mg, 0.97 mmol/g (theoretical loading), 0.097 mmol) in 3 mL of NMP was added 1-methylhomopiperazine (0.11 mL, 0.9 mmol), DIEA (0.16 mL, 0.9 mmol), and PyBOP (0.23 g, 0.45 mmol). The mixture was shaken at rt for overnight. The resin was washed with NMP (20 mL x 2), DCM (20 mL x 2), MeOH (20 mL x 2), DCM (20 mL x 2), and dried in vacuum oven at 35 °C for overnight. An analytical amount of the resin was cleaved with 20% of TFA in DCE for 10 min. The resulting solution was concentrated *in vacuo* and dissolved in 0.5 mL of MeOH. MS (ESI): 472 $[M+H]^+$.

To a mixture of the above resin-bound *N*-({3'-[(4-methylhexahydro-1*H*-1,4-diazepin-1-yl)carbonyl]-3-biphenylyl}methyl)-1,3-benzodioxole-5-

carboxamide (100 mg, 0.89 mmol/g (theoretical loading), 0.089 mmol) in 6 mL of CH_3CN was added MeI (0.05 mL). The mixture was shaken at rt for overnight. The resin was washed with CH_3CN (20 mL x 2), DCM (20 mL x 2), MeOH (20 mL x 2), DCM (20 mL x 2), and dried in vacuum oven at 35 °C for overnight. The resin was cleaved with 3 mL of 20% of TFA in DCE for 30 min and treated again with 3 mL of 20% of TFA in DCE for 30 min. The combined cleavage solution was concentrated *in vacuo*. The residue was dissolved in DMSO and purified using a Gilson semi-preparative HPLC system with a YMC ODS-A (C-18) column 50 mm by 20 mm ID, eluting with 10% B to 90% B in 3.2 min, hold for 1 min where A = H_2O (0.1% trifluoroacetic acid) and B = CH_3CN (0.1% trifluoroacetic acid) pumped at 25 mL/min, to produce 4-[(3'-{[(1,3-benzodioxol-5-ylcarbonyl)amino]methyl}-3-biphenylyl)carbonyl]-1,1-dimethylhexahydro-1*H*-1,4-diazepin-1-ium trifluoroacetate - trifluoroacetic acid (1:1) (white powder, 8.4 mg, 28% over 6 steps). MS (ESI): 486 $[M]^+$.

BIOLOGICAL EXAMPLES

The inhibitory effects of compounds at the M_3 mAChR of the present invention are determined by the following *in vitro* and *in vivo* assays:

Analysis of Inhibition of Receptor Activation by Calcium Mobilization:

1) 384-well FLIPR assay

A CHO (chinese hamster ovary) cell line stably expressing the human M3 muscarinic acetylcholine receptor is grown in DMEM plus 10% FBS, 2 mM Glutamine and 200 ug/ml G418. Cells are detached for maintenance and for plating in preparation for assays using either enzymatic or ion chelation methods. The day before the FLIPR (fluorometric imaging plate reader) assay, cells are detached, resuspended, counted, and plated to give 20,000 cells per 384 well in a 50 ul volume. The assay plates are black clear bottom plates, Becton Dickinson catalog number 35 3962. After overnight incubation of plated cells at 37 degrees C in a tissue culture incubator, the assay is run the next

day. To run the assay, media are aspirated, and cells are washed with 1x assay buffer (145mM NaCl, 2.5mM KCl, 10mM glucose, 10mM HEPES, 1.2 mM $MgCl_2$, 2.5mM $CaCl_2$, 2.5mM probenecid (pH 7.4.) Cells are then incubated with 50ul of Fluo-3 dye (4uM in assay buffer) for 60 – 90 minutes at 37 degrees C. The calcium- sensitive dye allows cells to exhibit an increase in fluorescence upon response to ligand via release of calcium from intracellular calcium stores. Cells are washed with assay buffer, and then resuspended in 50ul assay buffer prior to use for experiments. Test compounds and antagonists are added in 25 ul volume, and plates are incubated at 37 degrees C for 5 -30 minutes. A second addition is then made to each well, this time with the agonist challenge, acetylcholine. It is added in 25 ul volume on the FLIPR instrument. Calcium responses are measured by changes in fluorescent units. To measure the activity of inhibitors / antagonists, acetylcholine ligand is added at an EC_{80} concentration, and the antagonist IC_{50} can then be determined using dose response dilution curves. The control antagonist used with M3 is atropine.

2) 96-well FLIPR assay

Stimulation of mAChRs expressed on CHO cells were analyzed by monitoring receptor-activated calcium mobilization as previously described . CHO cells stably expressing M_3 mAChRs were plated in 96 well black wall/clear bottom plates. After 18 to 24 hours, media was aspirated and replaced with 100 µl of load media (EMEM with Earl's salts, 0.1% RIA-grade BSA (Sigma, St. Louis MO), and 4 µM Fluo-3-acetoxymethyl ester fluorescent indicator dye (Fluo-3 AM, Molecular Probes, Eugene, OR) and incubated 1 hr at 37° C. The dye-containing media was then aspirated, replaced with fresh media (without Fluo-3 AM), and cells were incubated for 10 minutes at 37° C. Cells were then washed 3 times and incubated for 10 minutes at 37° C in 100 µl of assay buffer (0.1% gelatin (Sigma), 120 mM NaCl, 4.6 mM KCl, 1 mM KH_2PO_4, 25 mM $NaHCO_3$, 1.0 mM $CaCl_2$, 1.1 mM $MgCl_2$, 11 mM glucose, 20mM HEPES (pH 7.4)). 50 µl

of compound ($1x10^{-11}$ – $1x10^{-5}$ M final in the assay) was added and the plates were incubated for 10 min. at 37° C. Plates were then placed into a fluorescent light intensity plate reader (FLIPR, Molecular Probes) where the dye loaded cells were exposed to excitation light (488 nm) from a 6 watt argon laser. Cells were activated by adding 50 µl of acetylcholine (0.1-10 nM final), prepared in buffer containing 0.1% BSA, at a rate of 50 µl/sec. Calcium mobilization, monitored as change in cytosolic calcium concentration, was measured as change in 566 nm emission intensity. The change in emission intensity is directly related to cytosolic calcium levels . The emitted fluorescence from all 96 wells is measured simultaneously using a cooled CCD camera. Data points are collected every second. This data was then plotting and analyzed using GraphPad PRISM software.

Methacholine-induced bronchoconstriction

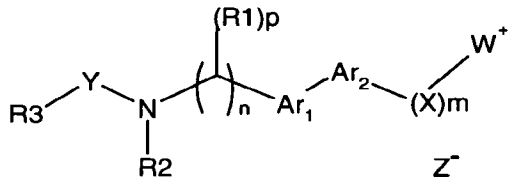
Airway responsiveness to methacholine was determined in awake, unrestrained BalbC mice ($n = 6$ each group). Barometric plethysmography was used to measure enhanced pause (Penh), a unitless measure that has been shown to correlate with the changes in airway resistance that occur during bronchial challenge with methacholine . Mice were pretreated with 50 µl of compound (0.003-10 µg/mouse) in 50 µl of vehicle (10% DMSO) intranasally, and were then placed in the plethysmography chamber. Once in the chamber, the mice were allowed to equilibrate for 10 min before taking a baseline Penh measurement for 5 minutes. Mice were then challenged with an aerosol of methacholine (10 mg/ml) for 2 minutes. Penh was recorded continuously for 7 min starting at the inception of the methacholine aerosol, and continuing for 5 minutes afterward. Data for each mouse were analyzed and plotted by using GraphPad PRISM software.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is:

1. A compound according to formula I herein below:



(I)

wherein

Ar1 and Ar2, are independently, selected from the group consisting of optionally substituted phenyl and optionally substituted monocyclic heteroaryl;

W^+ is $N^+R_6R_7R_8$, or an optionally substituted saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more quaternary ammonium nitrogens, and optionally contain one or more O, or S;

Z^- is a pharmaceutically acceptable counter ion, selected from the group consisting of I^-, Br^-, Cl^-, F^-, $CF3COO^-$, mesylate, and tosylate;

X is C(R1)p, or C(O); wherein, when X is C(R1)p, m is an interger from 0 to 3; when X is C(O), m is 1;

p is an interger from 0 to 2;

n is an interger from 0 to 3;

Y is C(O), S(O)q, HNC(O), or OC(O); wherein, q is 1 or 2;

R1 and R2 are independently selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted heterocylic, optionally substituted heterocyclicalkyl, optionally substituted alkenyl, optionally substituted aryl, optionally substituted aryl alkyl, optionally substituted heteroaryl, and optionally substituted heteroaryl alkyl;

R3 is selected from the group consisting of optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkenyl, optionally substituted C_1-C_{10} alkyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted aryl alkyl, and optionally substituted heteroaryl alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of halogen, cyano, hydroxy, hydroxy substituted C_{1-10}alkyl, C_{1-10} alkoxy, $S(O)_{m'}$ C_{1-10} alkyl, C(O)R4, $C(O)NR_4R_5$; C(O)OH; $S(O)_2NR_4R_5$, $NHC(O)R_4$, $NHS(O)_2R_4$, C_{1-10} alkyl, alkenyl, halosubstituted C_{1-10} alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroaryl alkyl, wherein these aryl or heteroaryl moieties may be substituted one to two times by halogen, hydroxy, hydroxy substituted alkyl, C_{1-10} alkoxy, $S(O)_{m'}C_{1-10}$ alkyl, C_{1-10} alkyl, or halosubstituted C_{1-10} alkyl;

m' is 0, 1, or 2;

R_4 and R_5, are independently, selected from the group consisting of hydrogen, optionally substituted C_{1-10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted aryl, optionally substituted aryl alkyl, optionally substituted heteroaryl, and optionally substituted heteroaryl alkyl; or R_4 and R_5 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O, and S; and

R_6, R_7, and R_8, are independently, selected from the group consisting of hydrogen, optionally substituted C_{1-10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl,

optionally substituted heterocyclic, and optionally substituted heterocyclicalkyl; or R_7 and R_8 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O, N and S;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 selected from the group consisting of:

Ar1 and Ar2, are independently, selected from the group consisting of optionally substituted phenyl and optionally substituted monocyclic heteroaryl;

W^+ is an optionally substituted saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more quaternary ammonium nitrogens;

Z^- is a pharmaceutically acceptable counter ion, selected from the group consisting of I^-, Br^-, Cl^-, F^-, $CF3COO^-$, mesylate, and tosylate;

X is C(R1)p, m is 1;

p is 2;

n is an interger from 1 to 3;

Y is C(O), or S(O)q;wherein, q is 1 or 2;

R1 is hydrogen;

R2 is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted heterocylic, optionally substituted heterocyclicalkyl, optionally substituted aryl, optionally substituted aryl alkyl, optionally substituted heteroaryl, and optionally substituted heteroaryl alkyl;

R3 is selected from the group consisting of optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkenyl, optionally substituted C_1-C_{10} alkyl, optionally substituted C_3-C_{10} cycloalkyl, and optionally substituted C_3-C_{10} cycloalkyl alkyl; wherein, when substituted, a

group is substituted by one or more radicals selected from the group consisting of halogen, cyano, hydroxy, hydroxy substituted C_{1-10}alkyl, C_{1-10} alkoxy, $S(O)_{m'}$ C_{1-10} alkyl, C(O)R4, $C(O)NR_4R_5$; C(O)OH; $S(O)_2NR_4R_5$, $NHC(O)R_4$, $NHS(O)_2R_4$, C_{1-10} alkyl, alkenyl, halosubstituted C_{1-10} alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroaryl alkyl, wherein these aryl or heteroaryl moieties may be substituted one to two times by halogen, hydroxy, hydroxy substituted alkyl, C_{1-10} alkoxy, $S(O)_{m'}C_{1-10}$ alkyl, C_{1-10} alkyl, or halosubstituted C_{1-10} alkyl; and m' is 0, 1, or 2;

R_4 and R_5, are independently, selected from the group consisting of hydrogen, optionally substituted C_{1-10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted aryl, optionally substituted aryl alkyl, optionally substituted heteroaryl, and optionally substituted heteroaryl alkyl; or R_4 and R_5 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O, and S; and

R_7 and R_8, are independently, selected from the group consisting of hydrogen, optionally substituted C_{1-10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, and optionally substituted heterocyclicalkyl; or R_7 and R_8 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O, N and S;

or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 selected from the group consisting of:

Ar1 and Ar2, are independently, optionally substituted phenyl;

W^+ is an optionally substituted saturated or partially unsaturated 5-8 membered ring system in which one or more rings contain one or more quaternary ammonium nitrogens;

Z^- is a pharmaceutically acceptable counter ion, selected from the group consisting of I^-, Br^-, Cl^-, F^-, $CF3COO^-$, mesylate, and tosylate;

X is C(R1)p;

R1 is hydrogen

p is 2;

m is 1;

n is 1;

Y is C(O), or S(O)q; wherein, q is 1 or 2;

R2 is selected from the group consisting of hydrogen, optionally substituted C_1-C_{10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted heterocylic, optionally substituted heterocyclicalkyl, optionally substituted aryl alkyl, and optionally substituted heteroaryl alkyl;

R3 is selected from the group consisting of optionally substituted aryl, optionally substituted heteroaryl, optionally substituted alkenyl, optionally substituted C_1-C_{10} alkyl, optionally substituted C_3-C_{10} cycloalkyl, and optionally substituted C_3-C_{10} cycloalkyl alkyl; wherein, when substituted, a group is substituted by one or more radicals selected from the group consisting of halogen, cyano, hydroxy, hydroxy substituted C_{1-10}alkyl, C_{1-10} alkoxy, $S(O)_{m'}$ C_{1-10} alkyl, C(O)R4, $C(O)NR_4R_5$; C(O)OH; $S(O)_2NR_4R_5$, $NHC(O)R_4$, $NHS(O)_2R_4$, C_{1-10} alkyl, alkenyl, and halosubstituted C_{1-10} alkyl; wherein m' is 0, 1, or 2;

R_4 and R_5, are independently, selected from the group consisting of hydrogen, optionally substituted C_{1-10} alkyl, optionally substituted alkenyl,

optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted aryl, optionally substituted aryl alkyl, optionally substituted heteroaryl, and optionally substituted heteroaryl alkyl; or R_4 and R_5 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O, and S; and

R_7 and R_8, are independently, selected from the group consisting of hydrogen, optionally substituted C_{1-10} alkyl, optionally substituted alkenyl, optionally substituted C_3-C_{10} cycloalkyl, optionally substituted C_3-C_{10} cycloalkyl alkyl, optionally substituted aryl, optionally substituted arylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, optionally substituted heterocyclic, and optionally substituted heterocyclicalkyl; or R_7 and R_8 together with the nitrogen to which they are attached form a 5 to 7 member ring which may optionally comprise an additional heteroatom selected from O, N and S;

or a pharmaceutically acceptable salt thereof.

4. A compound according to claim 1 selected from the group consisting of:

1-methyl-1-({3'-[({[4-(methyloxy)phenyl]sulfonyl}amino)methyl]-3-biphenylyl}methyl)piperidinium trifluoroacetate;

1-[(3'-{[(1,3-benzodioxol-5-ylcarbonyl)amino]methyl}-3-biphenylyl)methyl]-1-methylpiperidinium trifluoroacetate;

1-[(3'-{[(1,3-benzodioxol-5-ylcarbonyl)amino]methyl}-3-biphenylyl)methyl]-1-methylpiperazin-1-ium trifluoroacetate - trifluoroacetic acid (1:1);

1,1-dimethyl-4-({3'-[({[4-(methyloxy)phenyl]sulfonyl}amino)methyl]-3-biphenylyl}methyl)piperazin-1-ium trifluoroacetate - trifluoroacetic acid (1:1);

4-[(3'-{[(1,3-benzodioxol-5-ylcarbonyl)amino]methyl}-3-biphenylyl)methyl]-1,1-dimethylpiperazin-1-ium trifluoroacetate - trifluoroacetic acid (1:1);

1-[(3'-{[(1,3-benzodioxol-5-ylcarbonyl)amino]methyl}-3-biphenylyl)methyl]-1-methyl-3-oxopiperazin-1-ium trifluoroacetate;

4-[(3'-{[(1,3-benzodioxol-5-ylcarbonyl)amino]methyl}-3-biphenylyl)carbonyl]-1,1-dimethylhexahydro-1*H*-1,4-diazepin-1-ium trifluoroacetate - trifluoroacetic acid (1:1); and

4-{[3'-({[(3-cyanophenyl)carbonyl]amino}methyl)-3-biphenylyl]methyl}-1,1-dimethylpiperazin-1-ium trifluoroacetate - trifluoroacetic acid (1:1);

or any other pharmaceutically acceptable counter ion and/or salt.

5. A pharmaceutical composition for the treatment of muscarinic acetylcholine receptor mediated diseases comprising a compound according to claim 1 and a pharmaceutically acceptable carrier thereof.

6. A method of inhibiting the binding of acetylcholine to its receptors in a mammal in need thereof comprising administering a safe and effective amount of a compound according to claim 1.

7. A method of treating a muscarinic acetylcholine receptor mediated disease, wherein acetylcholine binds to said receptor, comprising administering a safe and effective amount of a compound according to claim 1.

8. A method according to claim 8 wherein the disease is selected from the group consisting of chronic obstructive lung disease, chronic bronchitis, asthma, chronic respiratory obstruction, pulmonary fibrosis, pulmonary emphysema and allergic rhinitis.

9. A method according to claim 9 wherein administration is via inhalation via the mouth or nose.

10. A method according to claim 10 wherein administration is via a medicament dispenser selected from a reservoir dry powder inhaler, a multi-dose dry powder inhaler or a metered dose inhaler.

11. A method according to claim 11 wherein the compound is administered to a human and has a duration of action of 12 hours or more for a 1 mg dose.

12. A method according to claim 12 wherein the compound has a duration of action of 24 hours or more.

13. A method according to claim 13 wherein the compound has a duration of action of 36 hours or more.

ABSTRACT OF THE DISCLOSURE

Muscarinic Acetylcholine receptor antagonists and methods of using them are provided.